

CONTINUOUS TIME RANDOM WALK AND MIGRATION PROLIFERATION DICHOTOMY OF BRAIN CANCER

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Abstract

A theory of fractional kinetics of glial cancer cells is presented. A role of the migration-proliferation dichotomy in the fractional cancer cell dynamics in the outer-invasive zone is discussed and explained in the framework of a continuous time random walk. The main suggested model is based on a construction of a 3D comb model, where the migration-proliferation dichotomy becomes naturally apparent and the outer-invasive zone of glioma cancer is considered as a fractal composite with a fractal dimension $D_{\text{fr}} < 3$.

KEYWORDS: Glioma; Migration-Proliferation Dichotomy; Fractional Kinetics.

1 Introduction

Brain tumors result from the uncontrolled growth of abnormal cells, destruction of normal tissues, and invasion of vital organs. These processes can be subdivided into many types based on several classification characteristics and involve any of the cell types found in the brain, such as neurons, glial cells, astrocytes, or cells of the meninges [1, 2]. The mechanisms behind cancer progression result from the accumulation of one or a few specific mutations that disrupt biological pathways like growth factor signaling, DNA damage repair, cell cycle, apoptosis and cellular adhesion [3]. Among all possible cancer cell genotypes, leading to six main alternations of malignant growth [3], cell motility and invasion are the most important for the present consideration.

Glioma is one of the most recalcitrant brain disease, with an optimal therapy treatment survival period of 15 months and most tumors recur within 9 months of initial treatment [4, 5]. One of the main possible reason of such devastating manifestation is the migration proliferation dichotomy of cancer cells. This

phenomenon has been firstly observed at clinical investigations [6, 7], where it has been shown that in the outer invasive zone glioma cancer cells possesses a property of high motility, while the proliferation rate of these migratory cells is essentially lower than in the tumor core. This anti-correlation between proliferation and migration of cancer cells, also known as the Go or Grow hypothesis (see discussions in [8, 9]), suggests that cell division and cell migration are temporally exclusive phenotypes [6]. The phenomenon that tumor cells defer proliferation for cell migration was also experimentally demonstrated¹ in [10, 11, 12]. The switching process between these two phenotypes is still not well understood. Moreover, it should be mentioned that conflicting data appear in the literature concerning the Go or Grow hypothesis; details of discussions on this can be found in [8, 9].

Extensive theoretical modelling follow this finding. A switching process between these two phenotypes still is not well understood, and many efforts are directed to develop relevant models with relevant mechanisms of switching of the glioma cells, resulting in several phenomenological models. Comprehensive discussions of these models one can find in [14, 15, 16, 17, 18]. It was suggested by Khain *et al* [14, 19] that the motility of cancer cells is a function of their density. Multi-parametric modelling of the phenotype switching was considered in [20]. The agent-based approach to simulate multi-scale glioma growth and invasion was used in [21, 22]. Subdiffusive cancer development on a comb was studied in [23], where a continuous time random walk (CTRW) was firstly suggested for metastatic cancer development. A stochastic approach for the proliferation-migration switching involving only two parameters was proposed in [24, 25] where the transport of cancer cells was formulated in terms of the CTRW, as well. ‘Go or Grow’ mechanism was proposed in [15], where the transition to invasive tumor phenotypes can be explained on the basis of the oxygen shortage in the environment of a growing tumor. Phenotypic switching due to density effect was also suggested in [16, 26]. Both numerical and analytical approaches were developed in [17] to study the glioma propagation in the framework of reaction-diffusion equations, where the phenotype switching depends on oxygen in a threshold manner. Collective behavior of brain tumor cells under the hypoxia condition was studied in [27].

A new therapeutic method, recently suggested [28, 29, 30] for non-invasive treatment of glioma - brain cancer by a radio-frequency electric field, also opens new directions of understanding of glioma development. A specific task emerging here is whether this new medical technology is effective against invasive cells with a high motility, when a switching between migrating and proliferating phenotypes takes place. As well known, one of the main features of malignant brain cancer is the ability of tumor cells to invade the normal tissue away from the multi-cell tumor core, causing treatment failure [31]. This problem relates to modelling of the dynamics of cancer glial cells in heterogeneous media (as brain cancer is) in the presence of a radio-frequency electric field, which acts as a tumor

¹This kind of migration-proliferation dichotomy was also found at metastatic behavior of breast cancer [13].

treating field (TTF) [28, 29, 30]. As reported, this transcarnial treatment by the low-intensity (1-3 V/cm), intermediate-frequency (100-200kHz) alternating electric field, produced by electrode arrays applied to the scalp, destroys cancer cells that undergoing to division, while normal tissue cells are relatively not affected². An important result of this new technology treatment is increasing the survival period in twice [30]³.

Therefore, an essential question is how the TTF affects aggressive migrating cells in the outer-invasive region with a low-rate of proliferation. To shed light on this situation, a simplified toy model for glioma treatment by the TTF has been suggested in [32, 33], where a mathematical task of the migration-proliferation dichotomy was formulated in the framework CTRW [34, 35]. Note, that the simplest mathematical realization of the CTRW mechanism of the migration-proliferation dichotomy was introduced for a comb model [23]. In the framework of this toy model, it was possible to estimate the effectiveness of the TTF treatment in the outer-invasive region of the tumor development [32]. It has also been shown that while the TTF is highly effective in the multi-cell tumor core, its action is ineffective in the presence of the migration-proliferation dichotomy [32]. This result is mainly based on the 1D consideration, where the fractal cancer composite is embedded in the 1D space. In reality, the situation is much more complicated, since the fractal cancer composite in the outer-invasive region develops in the 3D space. As a result of this, the TTF efficiency depends on the fractal dimension of the cancer composite in the outer-invasive region. Therefore, a more realistic model to estimate a medical effect of brain cancer (glioma) treatment by the RF electric field is suggested [33]. This model is based on a construction of a 3D comb model for the cancer cells, where the outer-invasive region of glioma cancer is considered as a fractal composite embedded in the 3D space. In the framework of this 3D model it was shown that the efficiency of the medical treatment by the TTF depends essentially on the mass fractal dimension D_{fr} of the cancer in the outer-invasive region.

In this paper we follow a CTRW consideration, suggested in [23]. Description of fractional kinetics of glioma development under the TTF treatment in the framework of the one dimensional (1D) and the three dimensional (3D) comb models show that the efficiency of the medical treatment depends essentially on the mass fractal dimension of the cancer in the outer invasive zone [32, 33]. The aim of this research is understanding both the role of the migration-proliferation dichotomy in fractional cancer cell transport and its influence on a therapeutic effect due to the TTF.

²An explanation of this phenomenon in the electrostatic framework is vague, since for this weak RF electric field of the order of 1V/cm, the inter-bridge voltage between the daughter cells is of the order 10^{-3} V that is less than the voltage fluctuations related with the cell shape fluctuations.

³In the latest phase III trial study for TTF treatment for glioblastoma [5], the TTF treatment has median survival of 6.6 months versus 6 months of the chemotherapy treatment.

2 Self-Entrapping by Fission as Fractional Mechanism of Tumor Development

In this section we formulate the migration–proliferation dichotomy in the framework of the CTRW. A simplified scheme of cell dissemination through the vessel network was considered by means of the following two steps [23, 36]. The first step is a biological process of cell fission. The duration of this stage is \mathcal{T}_f . The second process is cell transport itself with duration \mathcal{T}_t . Therefore the cell dissemination is approximately characterized by the fission time \mathcal{T}_f and the transport time \mathcal{T}_t . During the time scale \mathcal{T}_f , the cells interact strongly with the environment and motility of the cells is vanishingly small. The duration of \mathcal{T}_f could be arbitrarily large. During the second time \mathcal{T}_t , interaction between the cells is weak and motility of the cells leads to cell invasion, which is a very complex process controlled by matrix adhesion [6]. It involves several steps including receptor-mediated adhesion of cells to extracellular matrix (ECM), matrix degradation by tumor-secreted proteases (proteolysis), detachment from ECM adhesion sites, and active invasion into intercellular space created by protease degradation. It is convenient to introduce a “jump” length X_t of these detachments as a distance which a cell travels during the time \mathcal{T}_t . Hence, the cells form an initial packet of free spreading particles, and the contribution of cell dissemination to the tumor development process consists of the following time consequences:

$$\mathcal{T}_f(1)\mathcal{T}_t(2)\mathcal{T}_f(3)\dots \quad (1)$$

There are different realizations of this chain of times, due to different durations of $\mathcal{T}_f(i)$ and $\mathcal{T}_t(i)$, where $i = 1, 2, \dots$. Therefore, one concludes that transport is characterized by random values $\mathcal{T}(i)$ which are waiting (or self-entrapping) times between any two successive jumps of random length $X(i)$. This phenomenon is known as a continuous time random walk (CTRW) [37]. It arises as a result of a sequence of independent identically distributed random waiting times $\mathcal{T}(i)$, each having the same PDF $w(t)$, $t > 0$ with a mean characteristic time T and a sequence of independent identically distributed random jumps, $x = X(i)$, each having the same PDF $\lambda(x)$ with a jump length variance σ^2 . It is worth mentioning that a cell carries its own trap, by which it is set apart from transport. This process of self-entrapping differs from the standard CTRW, where traps are external with respect to the transporting particles. The crucial point of the fractional transport is the power law behavior of the waiting time PDF

$$w(t) = \alpha\mathcal{T}/(1 + t/\mathcal{T})^{1+\alpha} \quad (2)$$

where $0 < \alpha < 1$ and \mathcal{T} is a characteristic time. In this case the averaged time is infinite. A proper explanation of eq. (2) can be the following quotation from Ref. [34]: “A process with the long tailed pausing time distribution would suffer a very sporadic behavior – long intermittencies may exist, followed by bursts of events. The more probable pauses between events would be short but occasionally very long pauses would exist. Given a long pause, there is still a

smaller but finite probability that an even longer one will occur. It is on this basis that one would not be able to measure a mean pausing time by examining data.” Some justification of eq. (2) for the fission times can be presented by proposing multi-time scales of self-entrapping. We can consider that self-entrapping for different generations of cells has different mean characteristic time scales, see Appendix A. One obtains that the PDF, which accounts for all exit events from proliferation occurring on all time scales, has the power law asymptotic of eq. (2). Obtained distribution of eq. (2) is valid, when cell transport is considered on a fractional subdiffusive structure such as a comb model.

3 Comb-Like Model with Proliferation

Fractional transport of cells, namely subdiffusion, can be described in the framework of the comb model [38]. The comb model is an example of subdiffusive 1d media where CTRW takes place along the x structure axis. Diffusion in the y direction plays the role of traps with the PDF of delay times of the form $w(t) \sim 1/(1 + t/\mathcal{T})^{3/2}$. A special behavior of diffusion on the comb structure is that the displacement in the x -direction is possible only along the structure axis (x -axis at $y = 0$). Thus, the diffusion coefficient in the x -direction is $D_{xx} = D\delta(y)$, while the diffusion coefficient in the transversal y -direction is a constant $D_{yy} = D_0$. A random walk on the comb structure is described by the distribution function $P = P(x, y, t)$ and the current

$$\mathbf{j} = (-\delta(y)D\frac{\partial P}{\partial x}, -D_0\frac{\partial P}{\partial y}).$$

The continuity equation with proliferation $C(P)$ yields the following Fokker-Planck equation

$$\frac{\partial P}{\partial t} - \delta(y)D\frac{\partial^2 P}{\partial x^2} - D_0\frac{\partial^2 P}{\partial y^2} = C(P), \quad (3)$$

where the diffusion coefficients can be related to the CTRW parameters $D = \sigma^2/\mathcal{T}$. The initial condition $P(x, y, 0) = P_0(x)\delta(y)$ is an initial distribution on the x axis, and the boundary conditions are taken on infinities $P(t) = P'(t) = 0$ for both the x and y coordinates. The primes denote the spatial derivatives.

It is convenient to work with dimensionless variables and parameters. In the case of normal diffusion, when $D_x = \text{const}$, the dimensionless time and coordinates are obtained by re-scaling with relevant combinations of the comb parameters D_x and D_0 . One obtains the following dimension variables for time $(D_0^3/D_x^2)t \rightarrow t$ and for the coordinates $D_0x/D_x \rightarrow x$, $D_0y/D_x \rightarrow y$.

We consider a possible mechanism of tumor cell proliferation. The term $C(P)$ in eq. (3) determines the change in the total number of transporting cells due to proliferation at rate \tilde{C} . This can be considered as a linear approximation of a logistic population growth [39]

$$C(P) = \tilde{C}P(1 - P/K), \quad (4)$$

where K is the carrying capacity of the environment (see *e.g.*, [40]). It is worth stressing that linearization is important in the use of the powerful machinery of the Laplace transform. When $P/K \rightarrow P < 1/2$ and $\mathcal{C} = K\tilde{\mathcal{C}}D_x^2/D_0^3$, then the linearization $C(P) = \mathcal{C}P$ is valid [39]. In the opposite case, when $P_1 > 1/2$ the growth is approximated by $C(P) = \mathcal{C}\bar{P}$, where $\bar{P} = 1 - P$. According to the migration–proliferation dichotomy in the comb model, the transporting cells along the x axis do not proliferate. This means that cells proliferate only if they have a non-zero y coordinate. Therefore, $C(P) = \mathcal{C}(1 - \delta(y))P$, and eq. (3) reads in the dimensionless form

$$\frac{\partial P}{\partial t} - \delta(y) \frac{\partial^2 P}{\partial x^2} - \frac{\partial^2 P}{\partial y^2} = \mathcal{C}(1 - \delta(y))P. \quad (5)$$

When $\mathcal{C} > 0$, eq. (5) describes cell transport with proliferation, and the PDF P corresponds to a low concentration of cells. In the opposite case, when $\mathcal{C} < 0$, eq. (5) describes fractional cell transport with degradation that corresponds to a high cell concentration, and P exchanges for \bar{P} .

The first term in the r.h.s. of eq. (5) is eliminated by substitution $P = e^{Ct}F$. Carrying out the Laplace transform $\tilde{F}(s, x, y) = \hat{\mathcal{L}}[F(x, y, t)]$ and looking for the solution in the form $\tilde{F} = e^{-\sqrt{s}|y|}f(x, s)$, one obtains

$$F(x, y, t) = \hat{\mathcal{L}}^{-1} [f(x, s) \exp(-\sqrt{s}|y|)] . \quad (6)$$

As admitted, the true motion is in the x axis, while the y axis is an auxiliary, and integration over y is performed. Integrating eq. (5) with respect to the variable y and introducing the PDF

$$P_1(x, t) = \int_{-\infty}^{\infty} P(x, y, t) dy, \quad (7)$$

one obtains the following equation for $F_1 = e^{-Ct}P_1$ in the Laplace space $\tilde{F}_1(s) = \hat{\mathcal{L}}[F_1(t)]$:

$$s\tilde{F}_1 - \partial_x^2 f = P_0(x) - \mathcal{C}f. \quad (8)$$

Integrating eq. (6) over y , we obtain a relation between the PDFs of the total number of cells F_1 and transporting number of cells f in the Laplace space

$$f \equiv \tilde{F}(x, y = 0, s) = (1/2)\sqrt{s}\tilde{F}_1(x, s).$$

Substitution of this relation in eq. (8) yields, after the Laplace inversion, the Fokker–Planck equation for the distribution F . To this end, eq. (8) is multiplied by \sqrt{s} and then by virtue of eq. (C. 6) the inverse Laplace transform yields the following equation for F_1

$$2D_C^{1/2}F_1 - \partial_x^2 F_1 = -\mathcal{C}F_1, \quad (9)$$

where D_C^α is the fractional derivative in the Caputo form [41, 42] (see Appendix C). This equation describes fractional transport of cells with fission when $\mathcal{C} > 0$ and degradation when $\mathcal{C} < 0$, where the sign of \mathcal{C} depends on either $P = e^{Ct}F < 1/2$, or $P > 1/2$ ⁴.

⁴Since $\partial\bar{P} = -\partial P$, eq. (5) for P (when $P < 1/2$) just coincides with one for $\bar{P} = 1 - P$

4 Fractional Dynamics of Untreated Cancer

As shown, the cell fission is a source of the fractional time derivatives. This equation can be extended for an arbitrary fractional exponent $0 < \alpha < 1$: $1/2 \rightarrow \alpha$. Therefore, this generalization of eq. (9) yields

$$D_C^\alpha F_1 - \alpha \partial_x^2 F_1 = -\alpha \mathcal{C} F_1. \quad (10)$$

Taking into account that D_C^α can be expressed by the Riemann–Liouville fractional derivatives D_{RL}^α (see Appendix C) $D_C^\alpha = D_{RL}^{\alpha-1} D_{RL}^1$ and $D_{RL}^{\alpha-1} D_{RL}^{1-\alpha} = 1$, we obtain another, standard, form for the fractional Fokker–Planck equation (FFPE) with proliferation, or degradation,

$$\frac{\partial F_1}{\partial t} - \alpha D_{RL}^{1-\alpha} \frac{\partial^2 F_1}{\partial x^2} = -\alpha \mathcal{C} D_{RL}^{1-\alpha} F_1. \quad (11)$$

To solve eq. (11), we use the separation of variables [35]. We consider an analytical solution for the $P < 1/2$ using the following substitution

$$F_1(x, t) = \sum_n T_n(t) \phi_n(x). \quad (12)$$

Therefore, a solution which corresponds to the initial condition $P_0(x)$, is determined by the Green function $G(x, t|x', 0)$:

$$F_1(x, t) = \int_{-\infty}^{\infty} dx' G(x, t|x', 0) P_0(x') = \int_{-\infty}^{\infty} dx' \int dk T_k(t) \phi_k(x) \phi_k^*(x') P_0(x'). \quad (13)$$

Here $\phi_k(x)$ is a solution of the eigenvalue problem

$$-\frac{\partial^2 \phi_k}{\partial x^2} = \lambda(k) \phi_k,$$

where $\lambda(k) = k^2$ is the continuous spectrum with eigenfunctions

$$\phi_k(x) = \exp[\pm kx]. \quad (14)$$

The temporal eigenfunction $T_k(t)$ is governed by the fractional equation

$$\dot{T}_k(t) + \alpha \lambda_C(k) D_{RL}^{1-\alpha} T_k(t) = 0, \quad (15)$$

where $\lambda_C(k) = (k^2 + \mathcal{C})$. The solution is described by the Mittag–Leffler function $E_\alpha(z) \equiv E_{\alpha,1}(z)$ [43] (see Appendix C)

$$T_k(t) = E_\alpha[\alpha \lambda_C(k) t^\alpha], \quad (16)$$

where $T_k(0) = 1$, and $E_\alpha(z)$ has the initial stretched exponent behavior

$$T_k(t) \sim \exp[-[\alpha \lambda_C(k) t^\alpha / \Gamma(1 + \alpha)]] \quad (17)$$

(when $P > 1/2$). The only difference is when $P < 1/2$, $\mathcal{C} > 0$, while for $P > 1/2$ one has $\mathcal{C} < 0$.

which turns over to the power law long-time asymptotics

$$T_k(t) \sim [\Gamma(1 - \alpha)\alpha\lambda_C(k)t^\alpha]^{-1}. \quad (18)$$

Using these properties of $E_\alpha(z)$, the fractional spreading of cancer cells can be evaluated analytically for both initial and long-time behaviors. Substitution of eqs. (14) and (17) in eq. (13) yields the following initial time solution

$$P_1(x, t) \propto \sqrt{\frac{\pi\Gamma(1+\alpha)}{\alpha t^\alpha}} \exp[\mathcal{C}t - \alpha\mathcal{C}t^\alpha/\Gamma(1+\alpha)] \\ \times \exp[-\Gamma(1+\alpha)x^2/4\alpha t^\alpha]. \quad (19)$$

Analogously, the long-time solution is

$$P_1(x, t) \propto \frac{1}{\alpha t^\alpha \Gamma(1-\alpha)} \exp[\mathcal{C}t - \sqrt{\mathcal{C}}|x|], \quad (20)$$

where we take, for clarity, $P_0 = \delta(x)$ for both the short and long time solutions. These two solutions (19) and (20) corresponds to different scales. Solution of eq. (20) describes long-time/sort-scale dynamics. When the argument in the exponential function is zero, it corresponds to the front of cell invasion with equation $x \sim l_0 = \sqrt{\mathcal{C}}t$. This is a so-called linear model which describes a solid tumor growth. In this region with $x < l_0$ the exponential growth $e^{\mathcal{C}t}$ is dominant. Sundiffusion described by eq. (19) corresponds to the cell transport in the outer-invasive zone with $x > l_0$. When $\mathcal{C} \rightarrow 0$ only this solution takes place. Therefore, we have the the cell spreading in the core region with $x < l_0$ is due to the cell proliferation, while in the outer-invasive zone the cell motility is the main engine of the cell spreading.

5 Cell Kinetics in Presence of the TTF

Let us consider cell kinetics in the outer-invasive zone in more detail. To this end we consider the fractal cancer development in the presence of the TTF. This process can be described by fractional kinetics in the framework of the comb model, as well, where it is easier to draw an intelligible picture of interplay between high-motility of aggressive cancer cells and the TTF in the outer-invasive region. Contrary to the 1D comb model, in this section we extend our consideration of the treated cancer to the three dimensional cancer development, where proliferation takes place inside a fractal composite, embedded in the 3D space with the fractal dimension $D_{\text{fr}} < 3$.

In the 3D comb model, this anomalous diffusion can be described by the 4D distribution function $P = P(\mathbf{x}, y, t)$, and by analogy with the 1D comb model (5), a special behavior here is the displacement in the 3D x -space at $y = 0$. The Fokker-Planck equation in the same dimensionless variables reads

$$\partial_t P = \delta(y)\Delta P + d\partial_y^2 P, \quad (21)$$

where d is an effective diffusion coefficient and $\Delta = \sum_{j=1}^3 \partial_{x_j}^2$.

5.1 Comb Model with Proliferation and TTF

Obviously, cell fission/division is random in the x -space and discontinuous, contrary to that in the tumor core. Therefore, the outer-invasive region of the cancer can be reasonably considered as a random fractal set $F_{D_{\text{fr}}}(\mathbf{x}) = F_{\alpha}(x_1) \times F_{\beta}(x_2) \times F_{\gamma}(x_3)$ embedded in the 3D space, as, for example, for low-grade astrocytomas [7], with the fractal dimension, $0 < D_{\text{fr}} < 3$ and $\alpha + \beta + \gamma = D_{\text{fr}}$. For simplicity, we take $\alpha = \beta = \gamma = D_{\text{fr}}/3 = \nu$.

The effective diffusion coefficient in eq. (21) becomes inhomogeneous $d \rightarrow d\chi(\mathbf{x})$, where $\chi(\mathbf{x}) = \chi(x_1)\chi(x_2)\chi(x_3)$ is a characteristic function of the fractal, such that $\chi(x_j) = 1$ for $x_j \in F_{D_{\text{fr}}}(\mathbf{x})$ and $\chi(x_j) = 0$ for $x_j \notin F_{D_{\text{fr}}}(\mathbf{x})$, where x_j are the Cartesian coordinates $j = 1, 2, 3$. Now we take into account the influence of the TTF that affects (destroys) only quiescent cells, belonged to the proliferation phenotype, according to Refs. [28, 29, 30]. Mathematically, this process is expressed by diffusion in the y direction with decay:

$$d \frac{\partial^2 P(\mathbf{x}, y, t)}{\partial y^2} \Rightarrow \chi(\mathbf{x}) [d \frac{\partial^2}{\partial y^2} - C] P(\mathbf{x}, y, t), \quad (22)$$

where coefficient C defines a difference between the proliferation and the degradation rate. In general case, C is a random function of time and space. For example, it was considered as a random death rate for the random walk in the discrete inhomogeneous media [44]. Here we take it as a positive averaged constant value.

Summarizing these arguments, mapping the glioma problem onto the 4D comb model can be described by the following rules. (i) The dynamics of cancer cells takes place in the 3D space, which is described by three x coordinates (x_1, x_2, x_3). (ii) The y axis corresponds to a supplementary coordinate that introduces the migration-proliferation dichotomy for the model. Therefore, at $y = 0$ the cells migrates and are not affected by the TTF. Contrarily, the cells with $y \neq 0$ proliferate and are subjected to the TTF.

Taking this into account, one arrives at the equation of the cancer development in the presence of the TTF

$$\frac{\partial P}{\partial t} = \delta(y) \Delta P + \chi(\mathbf{x}) [d \frac{\partial^2}{\partial y^2} - C] P(\mathbf{x}, y, t). \quad (23)$$

First, we apply the Fourier transform to eq. (23) with respect to the x_j coordinates. To this end, we rewrite eq. (23) in the form of convolution integrals.

Therefore, as shown in [33] and in Appendix B, fractal cancer development in the presence of the TTF can be considered as a random fractal composite of cancer cells embedded in the 3D. Following coarse graining and averaging procedure, described in Appendix B, we arrive at the 3D comb model that describes the fractal cancer development in the outer-invasive region of glioma in the presence of the TTF

$$\partial_t P(r, y, t) = \delta(y) \Delta P(r, y, t) + [d \partial_y^2 - C] (-\Delta)^{\frac{3-D_{\text{fr}}}{2}} P(r, y, t), \quad (24)$$

where $P(r, y, t)$ is the radial function in the 3D x space $r = |\mathbf{x}|$.

5.2 Dynamics in the Fourier-Laplace Space

Equation (24) can be considered as a starting point of the analysis, and its solution will be obtained by means of the Fourier and the Laplace transforms. Performing the Fourier transform, constructed in the Appendix B, one obtains eq. (24) in the Fourier space

$$\partial_t \bar{P} = -k^2 \delta(y) \hat{P} + k^{3-D_{\text{fr}}} [d \partial_y^2 \hat{P} - C \bar{P}]. \quad (25)$$

The last term in the r.h.s. of eq. (25) is eliminated by the substitution

$$\bar{P}(k, y, t) = \exp(-Ck^{3-D_{\text{fr}}}t) F(k, y, t) = e^{-Ck^{-\alpha}t} F(k, y, t), \quad (26)$$

where $\alpha = D_{\text{fr}} - 3$.

The next step of the analysis is the Laplace transform in the time domain

$$\hat{\mathcal{L}}[F(k, y, t)] = \tilde{F}(k, y, s).$$

Looking for the solution of the Laplace image in the form

$$\tilde{F}(k, y, s) = \exp[-|y|\sqrt{k^\alpha s/d}] f(k, s), \quad (27)$$

one arrives at the intermediate expression in the form of the Laplace and Fourier inversions

$$P(r, y, t) = \hat{\mathcal{F}}_k^{-1} \left\{ \exp(-Ck^{-\alpha}t) \hat{\mathcal{L}}_t^{-1} \left[\frac{e^{-|y|\sqrt{sk^\alpha/d}}}{2\sqrt{sd}k^{-\alpha} + k^2} \right] \right\}. \quad (28)$$

As admitted above, the y axis is the auxiliary, or supplementary coordinate, which determines the cell proliferating process (cell fission). Therefore to find the complete distribution of cancer cells in the x space, integration over y is performed (see Sec. 4):

$$\bar{P}(r, t) = \int_{-\infty}^{\infty} P(r, y, t) dy. \quad (29)$$

Both the integration over y and the inverse Laplace transform are carried out exactly. This, eventually, yields a solution in the form the 3D Fourier inversion

$$\bar{P}(r, t) = \frac{1}{(2\pi)^3} \int_{-\infty}^{\infty} e^{-i\mathbf{k} \cdot \mathbf{x}} \exp(-Ck^{3-D_{\text{fr}}}t) \mathcal{E}_{\frac{1}{2}} \left(-\frac{1}{2} \sqrt{k^{1+D_{\text{fr}}}t/d} \right) d^3k. \quad (30)$$

Here

$$\mathcal{E}_\alpha(-z) = \frac{1}{2\pi i} \int_\gamma \frac{u^{\alpha-1} e^u du}{u^\alpha + z}$$

is the Mittag-Leffler function defined by the inverse Laplace transform with a corresponding deformation of the contour of the integration [43].

5.3 True Distributions

Solution (30) is a convolution of the kernel of the TTF treatment $\mathcal{R}(z)$ and the untreated cancer distribution $\mathcal{P}(z)$

$$\overline{P}(r, t) = \mathcal{R} \star \mathcal{P}. \quad (31)$$

When $C = 0$, which means that the TTF compensates proliferation, the solution is described by the Mittag-Leffler function with the scaling variable $z = r/t^{\frac{1}{1+D_{\text{fr}}}}$. This scaling determines the cancer cell expansion

$$r \sim t^{\frac{1}{1+D_{\text{fr}}}} \quad (32)$$

that depends essentially on the fractal dimension of the proliferation volume of the fractal cancer composite and reflects the migration-proliferation dichotomy in the outer-invasive region. Indeed, for the fractal cancer volume (or mass) $\mu(r) \sim r^{D_{\text{fr}}}$, the cancer development is superdiffusive when $D_{\text{fr}} < 1$, while for $D_{\text{fr}} > 1$ the latter spreads subdiffusively. This property is pure kinetic and, apparently, is universal for the cancer development and related to the fractal dimension of the cancer [?].

Now let us return to the convolution integral (31). To avoid awkward expressions of integrations with the hypergeometric functions, we consider particular cases of the fractal dimension $D_{\text{fr}} = 2$ and $D_{\text{fr}} = 1$. For $D_{\text{fr}} = 2$, due to the scaling argument, one obtains that the untreated cancer spreads subdiffusively $\langle r^2 \rangle \sim t^{\frac{2}{3}}$, while for the TTF kernel we have

$$\mathcal{R}(r, t) = \frac{1}{\sqrt{(2\pi)^3 r}} \int_0^\infty e^{-Ctk} k^{\frac{3}{2}} J_{\frac{1}{2}}(kr) dk = \frac{1}{3\pi^2 (Ct)^3} {}_2F_1\left(\frac{3}{2}, 2; \frac{3}{2}; -\frac{r^2}{(Ct)^2}\right). \quad (33)$$

Here ${}_2F_1(a, b; c; z)$ is the hypergeometric function. This yields the power law decay of the distribution function

$$\mathcal{R}(r, t) = \frac{(Ct)^{-3} \pi^{-2}}{3[1 + r^2/(Ct)^2]^2}. \quad (34)$$

This power law kernel shows that the TTF is inefficient for $D_{\text{fr}} > 1$ in the presence of the migration proliferation dichotomy. It is tempting to calculate the second moment $\langle r^2(t) \rangle$ with the distribution $\overline{P}(r, t)$. In this case, one should recognize that a cutoff $r = t$ of the Lévy flights for $r, t \gg 1$ should be performed. This is a well known procedure [45], used for the Lévy walks.

5.3.1 $D_{\text{fr}} = 1$

The situation changes when $D_{\text{fr}} \leq 1$. In this case the TTF leads to the Brown exponential cutoff of the cancer spread in eq. (31). For $D_{\text{fr}} = 1$ the problem is analytically treatable. For the small argument, which corresponds (for a short time) to a long-scale tail of the distribution, the Mittag-Leffler function decays

exponentially $\exp\left(-K_{\frac{1}{2}}\sqrt{|k|^{1+D_{\text{fr}}}t}\right)$ [35, 43] with the generalized transport coefficient $K_{\frac{1}{2}} = [2\Gamma(3/2)\sqrt{d}]^{-1}$. This yields the solution for the compensated cancer with $C = 0$ in the form of the hypergeometric functions like in eqs. (33) and (34). Following [46], one obtains

$$\mathcal{P}(r, t) = \frac{K_{\frac{1}{2}}\sqrt{t}}{(2\pi)^3(1+r^2/K_{\frac{1}{2}}^2t)^2} \left[K_{\frac{1}{2}}\sqrt{t} + \sqrt{K_{\frac{1}{2}}^2t + r^2} \right]^{-\frac{1}{2}}. \quad (35)$$

This metastatic power law behavior is restricted by the Brown distribution due to the TTF kernel

$$\mathcal{R}(r, t) = \hat{\mathcal{F}}^{-1}[e^{-Ck^2t}] = \frac{1}{(4\pi Ct)^{3/2}} \exp\left(-\frac{r^2}{4Ct}\right). \quad (36)$$

The second moment is a good characteristic to show the TTF influence. One obtains from eq. (35) for the compensated cancer $\langle r^2 \rangle \sim t^{\frac{3}{2}}$ for $r \gg 1$ that corresponds to superdiffusion at the large scale asymptotics, and the cutoff at $r = t$ is taken into account. The same calculation with the TTF kernel yields an effective treatment with $\langle r^2 \rangle \sim t^{\frac{3}{4}}$ that corresponds to the superdiffusion–subdiffusion transition due to the TTF. Obviously, that untreated cancer with $C < 0$ leads to the exponential spreading of cancer cells due to the exponential proliferation.

5.4 Numerical Estimations of Eq. (30)

As shown in eqs. (34) and (36) analytical form of the TTF operator depends on fractal dimension D_{fr} . Since analytical estimation of eq. (30) leads to awkward expressions of integrations with the hypergeometric functions, numerical procedure is performed. The results are depicted in Fig. 1 for different values of the fractal dimension D_{fr} .

As obtained, the maximal therapeutic effect takes place at $D_{\text{fr}} = 3$ that immediately follows from eq. (30). One should recognize that the solution for the compensated cancer $\mathcal{P}(r, t)$ is exactly the form of the interplay between the TTF and subdiffusion, which is the result of the migration-proliferation dichotomy. Another manifestation of this interplay is the fractal dimension $D_{\text{fr}} < 3$ that leads to metastatic behavior of either the TTF kernel or compensated cancer solution.

6 Conclusion

The present study focuses on the influence of cell proliferation on transport properties. The mathematical formulation of this proliferation-migration dichotomy is based on the two main stages: cell fission with the self-entrapping time \mathcal{T}_f and cell transport with durations \mathcal{T}_t . By virtue of these two time scales a description of tumor development is reduced to a CTRW process. A toy model

of cancer development is suggested by using heuristic arguments on the relation between tumor development and the CTRW. In this case a fractional tumor development becomes a well defined problem since a mathematical apparatus of CTRW is well established (see *e.g.* [35, 34, 41, 47]). The constructed model is a modification of a so-called comb structure [38]. An important feature of this consideration of cell transport in the framework of the comb model is an essential enhancement of anomalous transport due to proliferation. Moreover, we obtained that the distribution function of the fractional transport depends on only two parameters, namely, scaled proliferation rate \mathcal{C} and the fractional exponent α , where $\alpha = 1/2$ for the comb model.

The next step is studying glioma cancer development in the outer-invasive region in the presence of a tumor treating field. The model is based on a construction of a 3D comb model for the cancer cell transport, where the outer-invasive region of glioma cancer is considered as a fractal composite, embedded in the 3D host of the normal cell tissues. The description is performed in the four-dimensional (\mathbf{x}, y) space, where the real three-dimensional \mathbf{x} space stands for the description of real cancer development, while the supplementary y -coordinate is introduced to describe a non-Markovian process in the framework of the Markovian description. From the biological point of view, this corresponds to the migration-proliferation dichotomy of the cancer cells, where the influence of the TTF is considered, as well. Therefore, the kinetic equation (24) in the (\mathbf{x}, y) space is constructed by means of the coarse-graining, or embedding procedure inside the fractal space. This corresponds to the averaging in the 3D Fourier space in eq. (B. 6), and can be (roughly) considered as a generalization of the 1D procedure, based on averaging extensive physical values and expressed by means of a smooth function over a Cantor set that, eventually, leads to fractional integration [48, 49].

The efficiency of the TTF is estimated in the form of the convolution in eqs. (30) and (31). These expressions describe the influence of the TTF on the cancer development. The efficiency of the medical treatment by the TTF depends essentially on the fractal dimension D_{fr} , and the TTF is the most efficient for $D_{\text{fr}} = 3$. But, in reality, the outer-invasive zone is a fractal composite with the fractal dimension $D_{\text{fr}} < 3$.

Another result relates to the spread of the compensated cancer, which is determined by eq. (32). This result reflects the migration-proliferation dichotomy, namely the dependence of the cancer cells spread on the fractal dimension of the proliferation volume. For example, the cancer development is superdiffusive when $D_{\text{fr}} < 1$, while for $D_{\text{fr}} > 1$ it spreads subdiffusively. This property is pure kinetic and, apparently, is universal for the cancer development with a variety of bio-chemical processes. Recently an experimental validation of this kind phenomenon has been obtained for the metastatic detaching under *in vitro* studying the breast cancer [13]. Important question here also is aging the treatment. Initial times of the cancer development and treatment are different, and the time difference is unknown. Moreover, since the TTF acts on the proliferating cells only, the migration proliferation dichotomy leads to a particular case of a more general problem of aging population splitting [50]. For the present analysis this

general approach [50, 51] can be important for understanding the efficiency of the TTF. This can be an interesting issue for future studies.

It is also worth noting that a general solution in the form of the convolution $\overline{P}(r, t) = \mathcal{R} \star \mathcal{P}$ makes it possible to consider the compensated cancer in a more general framework of the fractional Fokker-Planck equation, namely [52]

$$\partial_t^p \mathcal{P} = (-\Delta)^{\frac{q}{2}} \mathcal{P},$$

where Caputo fractional derivative ∂_t^p is responsible for the migration-proliferation dichotomy, while $q = q(D_{\text{fr}})$ reflects the fractal dimension of the tumor development in the outer-invasive region. In our case, $p = \frac{1}{2}$, according the comb model construction, while $q = (1 + D_{\text{fr}})/4$ is an universal parameter, which determines the fractional space derivative due to the fractal dimension of the quiescent/proliferating cancer cells. In general case, $p \in (0, 1)$, and it is determined by another way of the introduction of the supplementary variable y [44, 53].

In conclusion, we discuss briefly a possible direct experiment, confirming the existence of a fractal cancer composite in the outer-invasive region. Cancer was considered as a fractal composite where a random fractal inclusion of the cancer cells $F_{D_{\text{fr}}}(\mathbf{x}) = F_{\alpha}(x_1) \times F_{\beta}(x_2) \times F_{\gamma}(x_3)$ is embedded in the 3D space of normal tissue cells. Therefore, in the presence of the TTF, one can consider the frequency-dependent permittivities of migrating cancer cells ε_m and the normal tissue cells ε_n [32]. Under certain frequency of the TTF, the condition $\varepsilon_m < \varepsilon_n$ can be fulfilled. These permittivities were observed in time domain dielectric spectroscopy in experimental studies of the static and dynamic dielectric properties of normal, transformed, and malignant B- and T-lymphocytes [57]. The solution of the Maxwell equation for the electrostatic field in the frequency domain yields an essential enhancement of the respond field inside the random fractal dielectric composite of cancer cells. Therefore, the respond electric field can be large enough to break the cell membrane. For example, as shown in [32] the electric field response can be of the order of $10^4 \div 10^5$ V/cm, which exerts the irreversible electroporation [58] due to the external TTF with amplitude ~ 1 V/cm. This can be a mechanism for ablation of cancer cells, which effectively acts on migratory cancer cells.

A key quantity of this cancer treatment is localization of the electroporation field inside the cancer. There is a straightforward analogy with nanoplasmonics (see *e.g.*, [59, 60]), where the electric field enhancement is due to a so-called surface-plasmon resonance for a metal-dielectric composite, and localized surface plasmon oscillations are charge density oscillations confined to the conducting fractal nanostructure. The essential difference is that this biological cell enhancement of the electric field is not resonant, but geometrical due to the fractal cancer structure [61]. In this connection, *in vitro* experiments can be important for further understanding the interplay between the TTF and the migration-proliferation dichotomy. Theoretical description of this phenomenon needs more realistic assumptions than those suggested here in the framework of the comb model. Such studies should be performed in the framework of more

sophisticated models of the switching between the migration and proliferation phenotypes [14, 15, 16, 17, 18, 24, 25], and the next step is understanding how dielectric properties of cells correlate with cell motility and cell fission. Such experimental studies of the glioma cells can not be overestimated.

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A Power Law PDF

As an example, we consider that j -th generation of self-entrapping is the Poisson process

$$w_j(t) = \tau_j^{-1} \exp(-t/\tau_j)$$

with the characteristic time scale $\tau_j = \tau^j$, where $\tau = \tau_1 = \mathcal{T}$ is now an average time of cell divisions for the first generation. Therefore, following [54, 55] and repeating exactly the analysis of Ref. [55], we obtain, by taking into account events occurring on all time scales, the following distribution:

$$w(t) = \frac{1-b}{b} \sum_{j=1}^{\infty} b^j \tau^{-j} \exp(-t/\tau^j),$$

where $b < 1$ is a normalization constant. Therefore, the last expression is a normalized sum and

$$w(t/\tau) = \tau w(t)/b - (1-b) \exp(-t/\tau)/b.$$

Using conditions $t \gg \tau > 1/b$, one obtains that at longer times $w(t/\tau) = \tau w(t)/b$. The last expression is equivalent to

$$w(t) \sim 1/t^{1+\alpha}, \quad (\text{A. 1})$$

where $\alpha = \ln(b)/\ln(1/\tau)$.

B Coarse-Graining Procedure of Fractal Cancer Composite

Using the auxiliary identity

$$\chi(x_j)f(x_j) \equiv \partial_{x_j} \int_{-\infty}^{x_j} \chi(y)f(y)dy \equiv -\partial_{x_j} \int_{x_j}^{\infty} \chi(y)f(y)dy$$

with the boundary conditions $P(x_i = \pm\infty) = 0$, this integration with the characteristic function can be carried out by means of a convolution [52, 56, 62].

Note, that

$$\int_{-\infty}^{\infty} \chi(y) f(y) dy = \sum_{x_j \in F_\nu} \int_{-\infty}^{\infty} f(y) \delta(y - x_j) dy,$$

where $\sum_{x_j \in F_\nu} \delta(y - x_j) = \mu'(x) \sim |x|^{\nu-1}$ is a fractal density, such that on the finite interval $(-x, x)$, the integral

$$\int_{-x}^x d\mu(y) \sim |x|^\nu$$

corresponds to the fractal volume. Therefore, due to Theorem 3.1 in Ref. [62] we have

$$\int_0^x f(y) d\mu(y) \simeq \frac{1}{\Gamma(\nu)} \int_0^x (x-y)^{\nu-1} f(y) dy,$$

which is defined for the finite fractal volume $\mu(x) \equiv \mu(x_j)$.

In what follows we will use the terminology and useful notations of fractional integration and differentiation [35, 41, 42, 47]. Fractional integration of the order of ν is defined by the operator (see Appendix C)

$$_{-\infty}I_x^\nu f(x) = \frac{1}{\Gamma(\nu)} \int_{-\infty}^x f(y) (x-y)^{\nu-1} dy, \quad (\text{B. 1})$$

$$_xI_\infty^\nu f(x) = \frac{1}{\Gamma(\nu)} \int_x^\infty f(y) (y-x)^{\nu-1} dy, \quad (\text{B. 2})$$

where $0 < \nu < 1$ and $\Gamma(\nu)$ is the Gamma function. By means of these fractional integration and differentiation (see Appendix C)

$$\mathcal{W}_-^{1-\nu} f(x) = \partial_x [_{-\infty}I_x^\nu f(x)], \quad (\text{B. 3})$$

$$\mathcal{W}_+^{1-\nu} f(x) = \partial_x [_xI_\infty^\nu f(x)], \quad (\text{B. 4})$$

one introduces the coarse-graining integration with the characteristic function in the form of the Riesz fractional derivative [56]

$$\chi(x_j) P(x, y, t) \Rightarrow [\mathcal{W}_-^{1-\nu} + \mathcal{W}_+^{1-\nu}] P(x_j, y, t) = \mathcal{W}^{1-\nu} P(x_j, y, t). \quad (\text{B. 5})$$

B.0.1 Random fractal composite

We consider a random fractal with an averaged volume, embedded in the $3D$, which is a function of a radius only $\mu(r) \sim r^{D_{\text{fr}}}$ [63, 64], where $r = \sqrt{\sum_j x_j^2}$. Therefore, the distribution function and the kernel of the fractional integration are the radial functions, and therefore, fractional integrations over the Cartesian coordinates x_j are substituted by integrations over the radial functions. This averaging procedure can be performed in the Fourier space as follows

$$\hat{\mathcal{F}} \left[\prod_j W^{1-\nu} P(r, y, t) \right] = \prod_j |k_j|^{1-\nu} \hat{P}(\{k_j\}, y, t) \Rightarrow k^{3-D_{\text{fr}}} \bar{P}(k, y, t), \quad (\text{B. 6})$$

where $k = \sqrt{\sum_j k_j^2}$ is the radius in the Fourier space and $\bar{P}(k, y, t) = \hat{\mathcal{F}}[P(r, y, t)]$. This averaging substitute in the $3D$ Fourier space is an extension of $1D$ embedding in the fractal, obtained in [62, 48], in agreement with Nigmatulin's arguments on a link between fractal geometry and fractional integro-differentiation [48, 49]. This is constituted in the procedure of averaging extensive physical values and expressed by means of a smooth function over a Cantor set that, eventually, leads to fractional integration [48, 49].

Note, that we did not use here any property of the kernel as a radial function that can be considered as the Riesz potential [42], as well

$$\prod_j \partial_{|x_j|} \prod_j \frac{1}{|x_j - x'_j|^{1-\nu}} \Rightarrow \frac{1}{|x - x'|^{6-D_{\text{fr}}}} = \frac{\gamma(\alpha)}{\left(\sqrt{\sum_j (x_j - x'_j)^2}\right)^{3-\alpha}}, \quad (\text{B. 7})$$

where $\alpha = D_{\text{fr}} - 3$ and $\gamma(\alpha) \equiv \gamma(D_{\text{fr}})$ is defined by Weber's integral

$$\int_0^\infty z^\beta J_\nu(z) dz = 2^\beta \Gamma\left(\frac{\nu + \beta + 1}{2}\right) / \Gamma\left(\frac{\nu - \beta + 1}{2}\right) \quad (\text{B. 8})$$

at the Fourier transform of the Riesz kernel

$$\hat{\mathcal{F}}[r^{\alpha-3}] = \frac{(2\pi)^{\frac{3}{2}}}{\sqrt{k}} \int_0^\infty r^{\alpha-\frac{3}{2}} J_{\frac{1}{2}}(rk) dr = \gamma(D_{\text{fr}}) k^{3-D_{\text{fr}}}. \quad (\text{B. 9})$$

Following [42] (ch. 25), we redefine $\prod_j W^{1-\nu}$ as the fractional degree of the Laplace operator $(-\Delta)^{-\alpha/2}$, namely

$$\prod_j W^{1-\nu} P(r, y, t) \Rightarrow \frac{1}{\gamma(\alpha)} \int \frac{P(r') \prod_j dx'_j}{|x - x'|^{3-\alpha}} \equiv (-\Delta)^{-\frac{\alpha}{2}} P(r, y, t). \quad (\text{B. 10})$$

This yields (see also [42])

$$\hat{\mathcal{F}}(-\Delta)^{-\frac{\alpha}{2}} P(r, y, t) = k^{-\alpha} \bar{P}(k, y, t). \quad (\text{B. 11})$$

Eventually, we arrive at the $3D$ comb model (24)

$$\partial_t P(r, y, t) = \delta(y) \Delta P(r, y, t) + [d\partial_y^2 - C](-\Delta)^{\frac{3-D_{\text{fr}}}{2}} P(r, y, t). \quad (\text{B. 12})$$

C Fractional Integro-Differentiation

Fractional integration of the order of α is defined by the operator

$${}_a I_x^\alpha f(x) = \frac{1}{\Gamma(\alpha)} \int_a^x f(y) (x-y)^{\alpha-1} dy, \quad (\text{C. 1})$$

where $\alpha > 0$, $x > a$ and $\Gamma(z)$ is the Gamma function. The fractional derivative is the inverse operator to ${}_a I_x^\alpha$ as ${}_a D_x^\alpha f(x) = {}_a I_x^{-\alpha}$ and ${}_a I_x^\alpha = {}_a D_x^{-\alpha}$. Its explicit form is

$${}_a D_x^{-\alpha} = \frac{1}{\Gamma(-\alpha)} \int_a^x f(y) (x-y)^{-1-\alpha} dy. \quad (\text{C. 2})$$

For arbitrary $\alpha > 0$ this integral diverges, and as a result of a regularization procedure, there are two alternative definitions of ${}_a D_x^{-\alpha}$. For an integer n defined as $n-1 < \alpha < n$, one obtains the Riemann-Liouville fractional derivative of the form

$${}_a D_{RL}^\alpha f(x) = (d^n/x^n) {}_a I_x^{n-\alpha} f(x), \quad (\text{C. 3})$$

and fractional derivative in the Caputo form

$${}_a D_C^\alpha f(x) = {}_a I_x^{n-\alpha} f^{(n)}(x). \quad (\text{C. 4})$$

When $a = -\infty$, the resulting Weyl derivative is

$$\mathcal{W}^\alpha \equiv -\infty D_W^\alpha = -\infty D_{RL}^\alpha = -\infty D_C^\alpha. \quad (\text{C. 5})$$

One also has $-\infty D_W^\alpha e^x = e^x$. This property is convenient for the Fourier transform

$$\hat{\mathcal{F}}[\mathcal{W}^\alpha f(x)] = (ik)^\alpha \hat{f}(k),$$

where $\hat{\mathcal{F}}[f(x)] = \hat{f}(k)$.

The Laplace transform can be obtained for Eq. (C. 4). If $\hat{L}f(t) = \tilde{f}(s)$ is the Laplace transform of $f(t)$, then

$$\hat{L}[D_C^\alpha f(t)] = s^\alpha \tilde{f}(s) - \sum_{k=0}^{n-1} f^{(k)}(0^+) s^{\alpha-1-k}. \quad (\text{C. 6})$$

We also note that

$$D_{RL}^\alpha[1] = \frac{t^{-\alpha}}{\Gamma(1-\alpha)}, \quad D_C^\alpha[1] = 0. \quad (\text{C. 7})$$

The fractional derivative of a power function is

$$D_{RL}^\alpha t^\beta = \frac{t^{\beta-\alpha} \Gamma(\beta+1)}{\Gamma(\beta+1-\alpha)}, \quad (\text{C. 8})$$

where $\beta > -1$ and $\alpha > 0$. The fractional derivative from an exponential function can be simply calculated as well by virtue of the Mittag-Leffler function (see *e.g.*, [41]):

$$E_{\gamma,\delta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\gamma k + \delta)}. \quad (\text{C. 9})$$

Therefore, from Eqs. (refB9) and (C. 9) we have the following expression

$$D_{RL}^\alpha e^{\lambda t} = t^\alpha E_{1,1-\alpha}(\lambda t). \quad (\text{C. 10})$$

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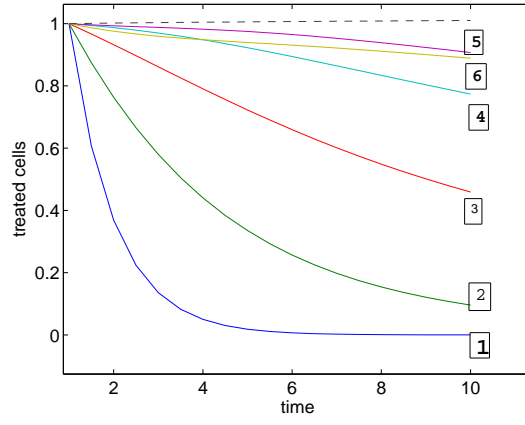


Figure 1: Dynamics of the treated cancer distribution for different values of the fractal dimension D_{fr} , where from plots from 1 to 6 correspond to $D_{\text{fr}} = (3, 2.5, 2, 1.5, 1, 0.5)$